Remarks

Applicants' claims 1 and 38-93 are pending in the identified patent application directed essentially to a method for regulating salt uptake and or release into or from the aqueous humor, wherein a controlling or modulating amount of a pharmaceutical composition, specifically an antiport modulator, is administered to ciliary epithelial cells of the aqueous humor (either *in vitro* or *in vivo* in the eye of a test animal or a human patient). The administered composition is a modulator of one or more antiports, wherein the one or more antiports are either a Na^+/H^+ exchanger or a Cl^-/HCO_3^- exchanger, or both, and the administered composition inhibits Na^+/H^+ exchange or Cl^-/HCO_3^- exchange – thereby regulating the salt uptake or release.

Claims 1, 68, 92 and 93 are presently amended, and claims 56-67 and 69-91 are cancelled. No substantive change has been made by amendment, and no new matter has been added to the application.

Response to the claim rejections under 35 USC §102.

The Examiner has maintained the earlier rejection of claims 1, 38-43 and 47-93 under 35 USC § 102(b) as anticipated by Drug Facts and Comparisons (1994). In making this rejection, the Examiner relies upon inherency of the prior art teaching of the presently claimed invention, even if the inherent principle of the disclosure was not recognized at the time it was made. The cited reference teaches that timolol, a beta blocker, may be used "to reduce elevated and normal ocular pressure with or without glaucoma," and thereby, in the view of the Examiner, the administration of a beta-blocker, inherently modulates the antiports, although such utility may not have been expressly recited or even recognized. The Examiner has reached this conclusion based upon the premise that modulation of the antiports in the ciliary epithelial cells of the aqueous humor of the eye is a *necessary consequence* of what was deliberately intended – which the Examiner states was in the case of the cited prior art to be a "modulation of aqueous secretion." Applicants respectfully question such a conclusion, and that while possible, such an effect was not a necessary or expected consequence at all – and therefore, it would not have been considered to be inherent.

In trying to look at this problem logically, the Examiner is directed first to the Background section of the specification, wherein the physical principles of how fluids are released into the aqueous humor is described. This is important because numerous cell types are

involved, and the ocular pressure represents a balance of a number of factors. As described at pages 1 and 2 of the specification:

> The secretion of aqueous humor into the eye results as a consequence of two opposing physiological processes: fluid secretion into the eye by the NPE cells and fluid reabsorption (secretion out of the eye) by the PE cells. Thus, both release of chloride ions by the NPE cells into the adjacent aqueous humor enhance secretion, and chloride ion release by the PE cells into the neighboring stroma reduces net secretion. Intraocular pressure reflects a balance between the rates of secretion and outflow of the aqueous humor. The aqueous humor leaves the eye in humans and primates primarily through the trabecular meshwork and canal of Schlemm, and in other mammals through the trabecular and angular aqueous plexus (references omitted).

Accordingly, the process in a human requires an interaction of all of the following elements: the outer pigmented ciliary epithelial (PE) cells facing the stroma, the inner nonpigmented ciliary epithelial (NPE) cells in contact with the aqueous humor, the trabecular meshwork and the canal of Schlemm. However, what was unknown until the present invention, was the significance of the antiports in controlling the balance of fluid between secretion and outflow by the ciliary epithelial cells and the trabecular network. Until one realizes that the antiports control the salt balance in the aqueous humor, one could not control those antiports to regulate salt uptake – which is the purpose of the present invention.

Applicants explained in the invention disclosure that four primary classes of drugs are currently used for the treatment of glaucoma and increased ocular pressure: miotics, sympathomimetics, beta-blockers,and carbonic anhydrase inhibitors. Moreover, Applicants explained that prior to the present invention, the most effective medical therapies using such drugs were aimed at reducing intraocular pressure by reducing the rate of flow of fluids *into* the eye, that is, by blocking unidirectional secretion from the stroma to the aqueous humor. However, prior to Applicants' invention, the importance of controlling the uptake of salts and the flow of through the antiports, and how to control those functions, was not known or understood.

At page 11, lines 20-23, Applicants teach:

> The present invention provides new understanding of the sodium/proton exchanger, and its functional relationship with the chloride/bicarbonate exchanger (the "antiports"), regarding the uptake of salts from the body into the PE cells.

The drug used in the Examiner's cited reference describes the use of timolol to reduce mean intraocular pressure (IOP) by 31% to 33%. However, because the cited reference offers no

description of the mode of how the timolol operates, it would be assumed that it operates in one of the many know ways to reduce IOP, typically by limiting the rate of flow of fluids into the eye. The cited prior use of timolol to reduce IOP does not indicate a modulation of the sodium/proton exchanger, and its functional relationship with the chloride/bicarbonate exchanger (the "antiports"), to control the uptake of salts from the body into the cilaiary epithelial cells . This was unknown until Applicants' invention. Applicants do not teach simply reducing IOP by previously known methods – which is the subject of the Examiner's cited reference.

The Examiner has concluded that simply because the same drug was used by Applicants and in the cited prior art, that all subsequent functions discovered for that drug are inherent. However, to make such an assumption would mean that if timilol is ultimated found to cure cancer, that such a function would also be inherent to administration of the drug. Yet, such an assumption of inherency goes far beyond what the law has defined inherency to mean.

As set forth in In re Oelrich, 212 USPQ 323, 326 (CCPA 1981), inherency may not be established by probabilities or possibilities. "The mere fact that a certain thing may result from a given set of circumstances is not sufficient [to establish inherency]." Id. Therefore, to be considered inherent, the result must, as pointed out by the Examiner, be a *necessary consequence* of the administration of the cited drug, it cannot simply be a possible or even probable effect.

Applicants acknowledge, and even explain in the specification, that known drugs, including timilol, reduce intraocular pressure. However, that is not Applicants' invention, and the knowledge in the prior art does not address or make inherent other unexpected functions that the drug *may* have. Such functions are not a *necessary consequence* of the previously known use; hence such functions are not inherent.

The claimed invention defines an entirely new function for a family of pre-existing known drugs. The safety of administering such drugs to the eye is demonstrated by their earlier known uses – but simply because the drugs can be safely used in the eye does not teach or suggest that they also regulate the salt uptake into (or release from) the ciliary epithelial cells via the antiports of those cells. Applicants' invention is not the control of IOP by simply limiting secretion of fluids into the eye, nor is it simply limiting fluid outflow. The inventors have, in fact, discovered a completed unexpected factor, which is the uptake of salts or their release in the aqueous humor.

One cannot conclude that simply because IOP is reduced by timilol administration, that as a necessary consequence, the drug also regulates the balance of salts in the eye, or that such regulation can be controlled by the regulation of the antiports. Before drawing the conclusion that the end result is inherent, the Examiner must first provide written evidence - other than Applicants' own specification - showing that the control of salt uptake in the ciliary epithelial cells is an inherent and necessary expectation associated with known uses of the known drug(s) to control IOP, and also that such uptake is controlled by modulating the antiports - let alone that one is a necessary consequence of the other. Unless such evidence is provided, the Examiner may not reject Applicants' invention on the erroneous assumption that timilol *may* inherently reduce IOP by modulating one or more antiports as described in the invention. This is particularly true when IOP may also be reduced by so many other mechanisms, and when timilol has many other uses. See also, Ex parte Skinner, 2 USPQ2d 1788, 1789 (BPAI 1987).

When all of the prior art is examined, the cited the prior art fails to define or even suggest Applicants' claimed invention regarding the specific regulation of salt uptake in the eye, meaning that the cited references fail to anticipate the invention. Applicants have kept the phrase "consisting essentially of" in the broadest claim, wherein it describes the composition being administered, since it is unlikely that such drugs could be administered to the eye without carrier, buffers and the like, which have no functional effect on the active agent. However, the regulating and administering steps are defined specifically, without use of the transition term "comprising." Consequently, it is clear that the cited reference fails to anticipate Applicants' invention under 35 USC § 102(b) since there is no indication in the reference, nor does it teach Applicants' method of regulating salt uptake in (or release from) the ciliary epithelial cells of the eye by modulating the function of the antiports of the aqueous humor. Accordingly, Applicants respectfully request that the rejection under 35 USC § 102(b) be reconsidered and withdrawn.

Response to the claim rejections under 35 USC §103.

The Examiner has maintained the rejection of claims 1, 38-41, 44-45, 49-50, 52-53, 55-63, 65-66, 68-76, 78-79, 8-87, 89-90 and 92-93 under 35 USC § 103 as obvious, over Burke (US Patent No. 5,215,99). In making this rejection, the Examiner states that although it fails to teach glaucoma, Burke teaches "methods and pharmaceutical compositions of Na^+/H^+ exchange inhibitors, which are employed to lower ocular pressure (IOP) and for the treatment of

intraocular hypertension (increased intraocular pressure)." In particular, the Examiner is concerned about the use of transition words in Applicants' claims. However, since the claims have been amended as described above, and the transition words are now removed or modified for the reasons stated above. Hence the rejection on that basis is now moot.

The Examiner further states that although Burke's invention was tested in a rabbit, such tests are acceptable for obviating Applicants' invention in a human. Applicants have previously submitted papers explaining why such a conclusion is not possible. In fact as explained above part of the balance system involved in the human (and mouse) eye is the trabecular mesh network. Aqueous humor flows out of the eye largely through the series arrangement of trabecular meshwork and then Schlemm's canal in primates, including humans. Although not intended to limit their invention, Applicants hypothesize that the enhancement of outflow may arise from the action of blockers of Na^+/H^+ exchange to shrink the trabecular meshwork cells (Mitchell, CH, Fleischhauer, JC, Stamer, WD, Peterson-Yantorno, K and Civan, MM, "Human trabecular meshwork cell volume regulation," Am. J. Physiol.: Cell Physiol. 283:C315-C326 (2002), thereby providing greater space around the cells for aqueous fluid to move to Schlemm's canal. Rabbits simply do not have a trabecular network in their eyes (see, for example, the Tamm article submitted in previous response), and therefore, Burke's use of rabbits cannot be considered to be an acceptable model animal to represent the response of a human eye to test drugs. Consequently, the broad statement Burke patent that blockers of Na^+/H^+ exchange, by themselves, do not lower IOP - is simply scientifically incorrect.

Therefore, contrary to the Examiner's comments, the cited reference, even when combined with other prior art cited by the Examiner fails to disclose, or even suggest, Applicants' invention. In fact, rather than teaching Applicants' claimed invention, as noted in the previous response, Burke actual confirms the unmet need in the art for such an invention. In two different points in the patent Burke states that the Na^+/H^+ exchange inhibitors, by themselves, do not work to lower IOP. See last paragraph of column 1, lines 56-60 ("It has now been discovered that Na^+/H^+ exchange inhibitors . . . although substantially inactive by themselves in lowering IOP . . ." and at the bottom of column 6, lines 63-65 ("Administration of three concentrations (0.1, 0.3, 1%) of the Na^+/H^+ exchange inhibitor did not significantly alter IOP (FIG. 1)." Consequently, Burke does not teach the use of Na^+/H^+ exchange inhibitors by themselves, rather Burke claims a method of lowering IOP by a co-administration of a IOP

lowering amount of an alpha-2 agonist and an amount of the Na^+/H^+ exchange inhibitor, amiloride or its analogs. Accordingly, Applicants' invention was not, at the time of the invention, obvious to one of ordinary skill in the art with any expectation of success, and the findings would have required undue experimentation.

By comparison, Applicants' claimed invention is actually in direct opposition to the Burke claims, and Burke teaches away from the present invention. Applicants have unequivocally demonstrated that the independent application of each of 3 different direct specific blockers of Na^+/H^+ exchange, by themselves, lower IOP in the mouse (See also, Avila, MY, Seidler, RW, Stone, RA and Civan, MM, "Inhibitors of NHE-1 Na^+/H^+ exchange reduce mouse intraocular pressure," Invest. Ophthalmol. Vis. Sci. 43:1897-1902 (2002)).

The Examiner has also rejected claim 46 under 35 USC § 103 as obvious, over Burke for the reasons stated in the previous argument, further in view of Scholtz *et al.* (US Patent No. 6,348,476). In making this rejection the Examiner relies on the teaching in Scholtz *et al.* that cariporide (not suggested in Burke) is an NHE inhibitor, and as such, cariporide could be used in the Burke invention to teach IOP reduction.

To the contrary, Scholtz *et al.* deals with a blocker of Na^+/H^+ exchange for treatment of cardiovascular diseases, but prior to Applicants' own work, there was no basis for presuming that blockers of Na^+/H^+ exchange would by themselves lower IOP. In fact, if one were to rely upon the Burke patent with which the Examiner suggests that Scholtz *et al.* be combined, one of ordinary skill in the art would have understood that blockers of Na^+/H^+ exchange by themselves could not lower IOP.

Thus, the deficiencies of Burke cannot been met by Scholtz *et al.* to teach Applicants' invention. Each cited reference fails to teach the independent use of an Na^+/H^+ exchange inhibitor to reduce IOP. Thus, even when combined, they cannot teach the formation of a polymeric vesicle, or Applicants' use thereof; and they cannot render Applicants' invention obvious.

Accordingly, in light of the overwhelming differences between the cited prior art and that of the present invention, the present invention quite simply operates in a completely different manner from the prior art. Thus, the prior art fails to render Applicants' invention obvious, and Applicants respectfully request that in light of the foregoing, the rejection under 35 USC § 103 be reconsidered and withdrawn.

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In sum, Applicants assert that all pending claims are in condition for allowance, and respectfully request that allowance be granted at the earliest date possible. Should the Examiner have any questions or comments regarding Applicants' amendments or response, she is asked to contact Applicants' undersigned representative at (215) 575-7034.

If there are any fees due in connection with the filing of this response, please charge the fees to our Deposit Account No. 50-0979.

Respectfully submitted,

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